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Multi-site Investigation of Outcomes with Implementation of *CYP2C19* Genotype-Guided Antiplatelet Therapy after Percutaneous Coronary Intervention

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Abstract

OBJECTIVES—This multi-center pragmatic investigation assessed outcomes following clinical implementation of *CYP2C19* genotype-guided antiplatelet therapy after PCI.

BACKGROUND—*CYP2C19* loss-of-function alleles impair clopidogrel effectiveness after percutaneous coronary intervention (PCI).

METHODS—After clinical genotyping, each institution recommended alternative antiplatelet therapy (prasugrel, ticagrelor) in PCI patients with a loss-of-function allele. Major adverse cardiovascular events (MACE, defined as myocardial infarction, stroke, or death) within 12 months of PCI were compared between patients with a loss-of-function allele prescribed clopidogrel versus alternative therapy. Risk was also compared between patients without a loss-of-function allele and loss-of-function allele carriers prescribed alternative therapy. Cox regression was performed, adjusting for group differences with inverse probability of treatment weights.

RESULTS—Among 1,815 patients, 572 (31.5%) had a loss-of-function allele. The risk for MACE was significantly higher in patients with a loss-of-function allele prescribed clopidogrel versus alternative therapy [23.4 vs. 8.7 per 100 patient-years; adjusted hazard ratio (HR): 2.26; 95% confidence interval (CI): 1.18 to 4.32; $p=0.013$]. Similar results were observed among 1,210 patients with an acute coronary syndrome at the time of PCI (adjusted HR: 2.87; 95% CI: 1.35 to 6.09, $p=0.013$). There was no difference in MACE between patients without a loss-of-function allele and loss-of-function allele carriers prescribed alternative therapy (adjusted HR: 1.14, 95% CI: 0.69 to 1.88, $p=0.60$).

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CONCLUSIONS—These data from real-world observations demonstrate a higher risk for cardiovascular events in patients with a *CYP2C19* loss-of-function allele if clopidogrel versus alternative therapy is prescribed. A future randomized study of genotype-guided antiplatelet therapy may be of value.

Keywords

clopidogrel; *CYP2C19*; pharmacogenomics; percutaneous coronary intervention; cardiovascular events; anti-platelet therapy

INTRODUCTION

Treatment with a P2Y₁₂ inhibitor plus aspirin is the standard of care following percutaneous coronary intervention (PCI) (1,2). The P2Y₁₂ inhibitor clopidogrel is a prodrug requiring bioactivation by cytochrome P450 (CYP) 2C19. *CYP2C19* loss-of-function (LOF) alleles lead to reduced or absent CYP2C19 activity, lower plasma concentrations of the clopidogrel active metabolite and reduced inhibition of platelet aggregation during clopidogrel therapy (3,4). Retrospective analyses from randomized clinical trials and patient registries have demonstrated a higher risk for major adverse cardiovascular events (MACE) in clopidogrel-treated patients with versus without a *CYP2C19* LOF allele, particularly after PCI (3,5–7).

Prasugrel and ticagrelor are alternative P2Y₁₂ inhibitors, shown to be superior to clopidogrel in preventing MACE in patients with an acute coronary syndrome (ACS) in the TRITON-TIMI 38 and PLATO trials, respectively (8,9). Post hoc genetic analyses from these trials showed no effect of *CYP2C19* genotype on outcomes with either prasugrel or ticagrelor (7,10). However, both drugs are more expensive than clopidogrel, which is available generically, and are associated with an increased bleeding risk. Ticagrelor is also associated with more frequent discontinuation due to side effects compared to clopidogrel (8).

While several institutions have implemented clinical *CYP2C19* genotyping to guide antiplatelet therapy selection after PCI (11–14), the impact of this strategy on clinical outcomes is not well defined. Therefore, among patients who underwent a PCI and clinical *CYP2C19* genotyping, we compared the risk for MACE between patients with a *CYP2C19* LOF allele prescribed clopidogrel 75 mg/day and those with a *CYP2C19* LOF allele prescribed alternative antiplatelet therapy. We also compared MACE risk between those with a LOF allele prescribed alternative therapy and those without a *CYP2C19* LOF allele treated with any P2Y₁₂ inhibitor.

METHODS

STUDY DESIGN

This was a multi-center investigation of clinical *CYP2C19* genotype-guided antiplatelet therapy post-PCI. The study design was pragmatic based on delivery of the genotype intervention as part of clinical care, the ultimate decision to order genetic testing and choice of drug therapy left to the discretion of the physician, unobtrusive collection of data from the electronic health record (EHR), and the focus on an objectively measured and clinically meaningful outcome (15–17). Seven institutions (University of Florida; University of North

Carolina, Chapel Hill; University of Maryland, Baltimore; University of Alabama, Birmingham; University of Illinois, Chicago; University of Pittsburgh; and Indiana University) implemented clinical *CYP2C19* genotyping with results returned via the EHR for consideration during antiplatelet therapy prescribing. All sites participated in the NIH-funded Implementing Genomics in Practice (IGNITE) Network Pharmacogenetics Working Group and contributed data (18). All patients from each site 18 years of age who underwent PCI and *CYP2C19* genotyping (per the strategy described in ONLINE TABLE 1) and received a P2Y₁₂ inhibitor after PCI were included, regardless of length of follow-up. A total of 1,815 patients across the seven institutions met these criteria and were included in the analysis.

CYP2C19 GENOTYPING AND PHENOTYPING

Genotyping was performed at each institution in a Clinical Laboratory Improvement Amendments (CLIA)-licensed laboratory, with the test ordered prior to or at the time of PCI. All sites genotyped for the LOF *CYP2C19**2 and *3 alleles, with additional rare alleles genotyped at 5 institutions (ONLINE TABLE 1). *CYP2C19* LOF allele status was defined by presence of at least one LOF allele.

CYP2C19 phenotype was assigned similarly across sites based on standardized definitions (19). Patients with one or two LOF alleles were assigned the intermediate metabolizer (IM) or poor metabolizer (PM) phenotype, respectively. Alternative antiplatelet therapy, consisting of prasugrel or ticagrelor in the absence of contraindications, was recommended for IMs and PMs, according to Clinical Pharmacogenetics Implementation Consortium guidelines (20). Ultimate antiplatelet therapy selection was left to the discretion of the prescriber.

DATA ABSTRACTION

Data abstraction procedures were approved by the Institutional Review Board at each institution. Clinical data at baseline and for up to 12 months following the index PCI, defined as the PCI performed in association with genotyping, were manually abstracted from the EHR through review of patient encounters, including the index PCI hospitalization and subsequent hospitalizations and outpatient visits, using a common data collection form (18). The occurrence of clinical outcomes of interest, including death, myocardial infarction (ST-segment or non-ST-segment elevation myocardial infarction), ischemic stroke, stent thrombosis, and unstable angina occurring over the 12-month period after the index PCI was determined. The date range for data abstraction was June 2012 through April 2016.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was the composite of MACE, defined as first occurrence of myocardial infarction, ischemic stroke, or death within 12 months following the index PCI (5). Secondary outcomes were the composite of MACE plus stent thrombosis and unstable angina and individual components of MACE. Outcomes were identified based on physician-reported diagnoses abstracted from the cardiac catheterization laboratory report, hospital discharge summary notes, or clinical notes in the event of death. Antiplatelet therapy was assessed at the time of event or last follow-up in which P2Y₁₂ inhibitor treatment was

documented. The number of days between the index PCI and initiation of alternative antiplatelet therapy was determined in patients with a LOF allele and was available for all but four patients.

STATISTICAL ANALYSIS

Data were curated and aggregated at the University of Florida. The time of index PCI was considered time zero. Patients who did not experience MACE during the 12 months post-PCI were censored at the time of the last EHR-documented follow-up in which treatment with a P2Y₁₂ inhibitor was documented. Event rates were calculated as number of events divided by follow-up time (time-to-event or censoring) and expressed as events per 100 patient-years.

Patient characteristics and PCI features at the time of the index PCI were compared between patients with a LOF allele prescribed either clopidogrel 75 mg/day (LOF-clopidogrel group) or alternative antiplatelet therapy (LOF-alternative group) by the Student's unpaired *t*-test, Chi-square analysis, or Fisher's exact test as appropriate. Additional comparisons were made between non-LOF patients prescribed clopidogrel or alternative antiplatelet therapy (non-LOF group) and LOF-alternative patients and between clopidogrel-treated versus alternatively treated-patients in the non-LOF group. All patients were included in the MACE outcome analyses. A pre-specified secondary analysis limited to patients with an ACS indication (ST-segment elevation or non-ST-segment elevation myocardial infarction or unstable angina) at the index PCI was also conducted.

Kaplan Meier plots were generated to estimate the cumulative risk of an event comparing patients in the LOF-clopidogrel versus LOF-alternative groups, and also patients in the non-LOF versus LOF-alternative groups. To adjust for differences between groups, we used logistic regression to estimate the probability (propensity score) of receiving clopidogrel versus alternative antiplatelet therapy using previously reported risk factors for cardiovascular events, and study site (2). Propensity scores were estimated separately for each comparison. Stabilized inverse probability of treatment weights (IPTW) were calculated using the estimated propensity score (21). Covariate balance between groups was assessed by examining the magnitude of any residual differences between groups after applying the weights. Differences were quantified as the weighted standardized differences, where a threshold of 10% was used to signify a meaningful difference in covariates (21). We also examined the weights themselves to ensure that no observations were overly influential. To compare risk for primary and secondary outcomes, we constructed cause-specific Cox proportional hazard models, weighted by IPTW. As a sensitivity analysis, we also estimated cluster robust standard errors by accounting for clustering by study site. All statistical analyses were performed in SAS (version 9.4, SAS Institute, Cary, North Carolina).

A total sample size of 1,815 patients, with at least 30% having an LOF allele and 60% of LOF allele carriers receiving alternative therapy, provided over 90% power with an alpha level of 0.05 to detect a hazard ratio of 2.0 for MACE between the LOF-clopidogrel and LOF-alternative groups.

RESULTS

PATIENT CHARACTERISTICS

Patient characteristics are summarized in Table 1. Among 1,815 patients, 1,210 (66.7%) presented with an ACS, and 1,793 (98.8%) had a stent placed at the time of PCI. The majority of patients received a drug eluting stent (83.6%), and were prescribed aspirin (98.2%) in addition to a P2Y₁₂ inhibitor.

Genotypes and associated phenotypes are shown in Online Table 2. The median time from index PCI to available genotype result was one day (interquartile range, IQR, one to three days). A LOF allele was present in 572 patients (31.5%; Figure 1, Online Table 2); 518 patients (28.5%) were IMs, and 54 patients (3%) were PMs. Alternative antiplatelet therapy was prescribed to a higher proportion of patients with a LOF allele (60.5%) compared to patients without a LOF allele (15.5%, $p<0.0001$, Figure 1). Fifty-eight percent of IMs and 87% of PMs were prescribed alternative antiplatelet therapy (Online Figure 1). Among patients with a LOF allele, the median time from genotype result to initiation of alternative antiplatelet therapy was one day (IQR: one to six days).

There were differences between the LOF-clopidogrel and LOF-alternative groups in age, prevalence of diabetes, stroke, peripheral vascular disease, and use of oral anticoagulation (Table 1). Age and prevalence of hypertension and diabetes differed between the non-LOF and LOF-alternative groups. These imbalances were negligible after adjustment with propensity score-derived IPTW (Table 2).

CLINICAL OUTCOMES

The median follow-up from index PCI to MACE or censoring was 4.8 months (IQR: 0.6 to 9.9 months). MACE was documented in 108 patients (5.95%) over the follow-up period (event rate of 13.5 per 100 patient-years). There was a higher rate of MACE in the LOF-clopidogrel group ($n=18$ events; event rate of 23.4 per 100 patient-years) compared to the LOF-alternative group ($n=16$ events; 8.7 per 100 patient-years; log rank $p=0.016$, Table 3, Figure 2). After propensity score adjustment, risk for MACE remained significantly higher in the LOF-clopidogrel versus LOF-alternative group (adjusted HR: 2.26; 95% CI: 1.18 to 4.32, $p=0.013$, Table 3). There was no difference in event rates between the non-LOF and LOF-alternative groups (13.7 versus 8.7 per 100 patient-years; log rank $p=0.15$; propensity score adjusted HR: 1.14; 95% CI: 0.69 to 1.88, $p=0.60$, Table 3). Similarly, within the non-LOF group, there was no difference in MACE rates between non-LOF patients treated with clopidogrel versus non-LOF patients treated with alternative therapy after adjusting for clinical differences between groups (adjusted HR: 1.01; 95% CI: 0.52 to 1.94, $p=0.98$, Online Tables 3 and 4). Accounting for within site clustering did not change the estimates for the primary outcome (Online Table 5).

In the 518 patients with the IM phenotype only, the risk for MACE was significantly higher with clopidogrel versus alternative antiplatelet therapy (log rank $p=0.003$, Online Figure 2), with event rates of 24.0 versus 6.7 per 100 patient-years, respectively. Only 7 of 54 PMs (13%) were treated with clopidogrel, precluding analysis of outcomes in this group.

Secondary outcomes are shown in Table 3. The risk for MACE plus other ischemic events (stent thrombosis and unstable angina) was higher in the LOF-clopidogrel versus LOF-alternative group (adjusted HR: 1.82; 95% CI: 1.07 to 3.12, $p=0.027$). There was no difference in MACE plus ischemic events between non-LOF and LOF-alternative groups (adjusted HR: 1.09; 95% CI: 0.72 to 1.63, $p=0.69$, Table 3) or between non-LOF patients treated with clopidogrel versus alternative therapy (adjusted HR: 1.02; 95% CI: 0.59 to 1.78, Online Table 3). Patients presenting with ACS at the time of index PCI (1,210 of 1,815 patients) contributed the majority of events to the analysis, including 86 of 108 (80%) MACE and 48 of 58 (83%) myocardial infarctions. Consistent with the analysis of the overall study population, among patients with ACS, the LOF-clopidogrel group had a higher rate of MACE compared to the LOF-alternative group (39.0 versus 8.9 per 100 patient-years, respectively; adjusted HR: 2.87; 95% CI: 1.35 to 6.09, $p=0.013$, Online Figure 3, Online Table 6). The risk of MACE plus other ischemic events (adjusted HR: 2.10; 95% CI: 1.12 to 3.90, $p=0.019$) was also significantly elevated. No differences in outcomes were observed between non-LOF and LOF-alternative groups in the ACS subset. Though not an outcome of the study, moderate and severe/life-threatening bleeding events, defined according to the GUSTO (Global Utilization of t-PA and Streptokinase for Occluded Coronary Arteries) criteria, were observed in 2.3% of patients in the overall study population and were similar across groups (22).

Based on the prevalence of patients with a LOF allele (31.5%), the number needed to genotype to identify a LOF allele carrier for whom alternative therapy would be recommended is 3.2. With an absolute difference in the proportion of patients who had a MACE in the LOF-clopidogrel (8.0%) and LOF-alternative (4.6%) groups (Table 3), the number of patients with a LOF allele needed to treat with alternative antiplatelet therapy to prevent one event is 29 (1/0.034). Therefore, the number of patients needed to genotype, with alternative antiplatelet therapy prescribed for all patients with a LOF allele, to prevent one cardiovascular event is 93 (29 times 3.2).

DISCUSSION

Our study is the first large multi-center study to examine outcomes after clinical implementation of *CYP2C19* genotype-guided antiplatelet therapy. We demonstrate the feasibility of genotype-guided antiplatelet therapy after PCI across multiple institutions, with efficient return of genotype results and high uptake of alternative antiplatelet therapy in patients with a LOF allele. More importantly, our results show a higher risk for MACE in patients with a *CYP2C19* LOF allele who are treated with clopidogrel versus alternative antiplatelet therapy. Most events occurred in patients with an ACS indication at the index PCI, in whom the risk for MACE was higher in LOF-clopidogrel versus LOF-alternative patients.

Retrospective genetic substudies of large clinical trials suggested worse outcomes in patients with a *CYP2C19* LOF allele treated with clopidogrel (3,5–7), but there is a paucity of data from large prospective clinical trials on outcomes with *CYP2C19* genotype-guided antiplatelet therapy. This has hindered inclusion of *CYP2C19* genotyping in clinical practice and PCI practice guidelines. Guidelines state that routine genetic testing is not

recommended, but might be considered in high-risk patients (Class IIb, Level of Evidence C) (1,2). A randomized controlled trial assessing the efficacy of genotype-guided antiplatelet therapy in a target population of over 5,000 patients began in 2013, but is not expected to be completed until 2020 (ClinicalTrials.gov Identifier NCT01742117). Given the magnitude, time, and expense of conducting traditional randomized controlled trials, other approaches are needed to generate an evidence base quantifying clinical outcomes related to pharmacogenetic-tailored therapy. Our pragmatic approach to assessing outcomes following clinical implementation of *CYP2C19* genotyping with real-world evidence is one such approach.

Our findings are in line with recent data from the Netherlands and Spain (23,24). The Netherlands study focused on patients undergoing elective PCI, who were clinically genotyped, with prasugrel recommended for PMs (23). Fewer adverse cardiovascular events were observed in PMs treated with prasugrel versus clopidogrel. The Spanish study included patients undergoing elective or emergent PCI, and recommendations for alternative therapy were made for both PMs and IMs (24). Compared to historic controls without genotyping, fewer adverse events were observed in patients receiving genotype-guided therapy. Our data are also consistent with those from two trials of Chinese patients undergoing PCI and randomized to either clopidogrel 75 mg/day or genotype-guided antiplatelet therapy, consisting of high dose clopidogrel (150 mg/day) for IMs and high dose clopidogrel plus cilostazol for PMs in one trial and ticagrelor for PMs in the other (25,26). Both studies observed a significant reduction in MACE in the genotype-guided arm.

The FDA-approved clopidogrel label warns of reduced clopidogrel effectiveness in PMs, and recommends consideration of alternative antiplatelet therapy in these patients, but is silent regarding risk and recommendations in IMs (27). In our study conducted in the context of routine clinical care, the majority of PMs (87%) were treated with alternative antiplatelet therapy, consistent with labeling recommendations, but a lower proportion of IMs were treated with alternative antiplatelet therapy (58%). This observation suggests that an IM test result is weighed less heavily than a PM result in the post-PCI antiplatelet therapy prescribing decision. However, when limiting our analysis to IMs, we observed a significantly higher rate of MACE with clopidogrel versus alternative antiplatelet therapy. These data indicate that IMs, like PMs, are at higher risk of adverse cardiovascular outcomes if treated with clopidogrel, and suggest that alternative antiplatelet therapy should be considered in both IMs and PMs.

Our real-world data corroborate those from retrospective analyses of clinical trials showing a higher risk for MACE among clopidogrel-treated patients with versus without a LOF allele (3,5–7). In the absence of a LOF allele, data from the TRITON-TIMI 38 trial also suggest that the risk for MACE may be comparable between clopidogrel and prasugrel, with a genetic substudy of the trial showing a relative risk for MACE of 0.98 (95% CI, 0.80–1.20) with prasugrel compared to clopidogrel in patients without a LOF allele. (28) The association between genotype and outcomes with clopidogrel appears to be indication specific, with strong and consistent associations in patients undergoing PCI, but not among lower-risk patients, such as those with atrial fibrillation or ACS managed medically (5,7,29,30). This is most clearly demonstrated in a meta-analysis showing an association

between *CYP2C19*LOF genotype and risk for MACE when analyzing studies of clopidogrel-treated patients undergoing PCI, but not when analyzing those without PCI (6).

Across institutions in our study, clopidogrel was the most commonly prescribed P2Y₁₂ inhibitor among patients without a *CYP2C19*LOF allele. This is consistent with other data suggesting that clopidogrel remains the predominant antiplatelet therapy in the U.S., prescribed 60% to 70% of the time according to published data through the first half of 2013 (31,32). To provide more contemporary use data, we interrogated practice patterns at Vanderbilt University Medical Center in the Southeastern U.S., and Sanford Medical Center, which draws patients from 6 states in the Midwestern U.S. Current practice patterns in these geographic locales demonstrate that clopidogrel remains commonly prescribed following PCI, regardless of clinical context. Specifically, among 10,115 patients who underwent PCI (41% with ACS) at Vanderbilt University Medical Center from 2010 to 2015, clopidogrel use fell minimally, from 93% to 72%, during that time (unpublished data). Similarly, among 1,260 patients from Sanford Medical Center who underwent PCI at 15 catheterization laboratories during the first 9 months of 2016, 53% with an ACS and 77% without ACS were discharged on clopidogrel (unpublished data).

Per PCI guidelines, the use of alternative antiplatelet agents in preference to clopidogrel after ACS and PCI is a Class IIa recommendation based on a moderate quality of evidence (1). In patients started on alternative P2Y₁₂ inhibitors according to PCI guidelines, *CYP2C19* genotype may still have an important role in informing therapy, especially after the 30-day post-PCI period when risk for events is highest (1). In patients with a high risk for bleeding or difficulty affording or tolerating newer agents, knowledge that a patient does not carry a LOF allele may give physicians increased confidence when considering switching the patient to the more affordable clopidogrel.

We did not directly assess why physicians chose to start some patients with a LOF allele on alternative therapy but not others. However, some speculation can be made based on prescribing patterns and characteristics of treatment groups. First, the higher use of alternative therapy in PMs versus IMs suggests that physicians may heed the boxed warning in the clopidogrel labeling and place a stronger emphasis on using alternative therapy in PMs, the focus of the boxed warning. Secondly, the higher prevalence of stroke or TIA history and concurrent anticoagulant use in the LOF-clopidogrel group versus the LOF-alternative group suggests that patient bleeding risk influenced preference for antiplatelet therapy.

LIMITATIONS

Our study has several limitations. First, there was no control group who did not undergo genotyping. However, some comparisons can be made with published event rates. In particular, in a genetic sub-study of the TRITON-TIMI 38 trial of patients with ACS and PCI, 8% of clopidogrel-treated patients without a LOF allele and 12% with a LOF allele had a MACE (3). Rates in our study were comparable, with a MACE occurring in 7% of ACS patients without a LOF allele (most of whom received clopidogrel) and 11% of clopidogrel-treated patients with a LOF allele. Secondly, genotype-guided therapy was not randomized, due to our pragmatic design, and antiplatelet therapy selection was left to physician

discretion. Thus, propensity scoring methods were used to mitigate the potential confounding effects related to differences across groups, and balance was achieved across comparison groups after weighting with IPTW. However, residual confounding regarding the choice of antiplatelet therapy may remain. Third, because ascertainment of outcomes was confined to the EHR without event adjudication, clinical events, including deaths, may have been missed. Fourth, length of follow-up was variable, as is typical for the clinical setting. As such, event rates were reported. Fifth, bleeding events were not objectively and systematically collected, given known difficulties in accurate bleeding assessment and the focus of data collection for this analysis on ischemic outcomes (33). Finally, because of the limited number of patients who underwent elective PCI, we did not examine outcomes separately in this group.

CONCLUSION

We demonstrate that implementation of clinical *CYP2C19* genotyping to guide post-PCI antiplatelet therapy is feasible across multiple institutions. Our data also demonstrate that cardiovascular outcomes were worse when clopidogrel versus alternative antiplatelet therapy was prescribed after PCI in patients with a LOF allele. The higher risk for MACE in LOF carriers prescribed clopidogrel was also evident when analyses were confined to ACS patients and, separately, to IMs (with a single LOF allele). Our data suggest that obtaining genotype data early after PCI allows identification of patients with a *CYP2C19* LOF allele in whom alternative antiplatelet therapy would reduce risk for events. A future randomized study of genotype-guided antiplatelet therapy may be of value.

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ABBREVIATIONS

ACS acute coronary syndrome

CYP	cytochrome P450
EHR	electronic health record
IGNITE	Implementing Genomics In Practice
IM	intermediate metabolizer
IPTW	inverse probability of treatment weights
LOF	loss-of-function
PCI	percutaneous coronary intervention
PM	poor metabolizer

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PERSPECTIVES

WHAT IS KNOWN?

CYP2C19 loss-of-function alleles impair clopidogrel activation and effectiveness after percutaneous coronary intervention. However, the impact of genotype-guided antiplatelet therapy on clinical outcomes is not well defined.

WHAT IS NEW?

This study demonstrates that patients with one or two *CYP2C19* loss-of-function alleles prescribed an alternative P2Y₁₂ inhibitor after PCI exhibit lower risk for cardiovascular events compared to patients with one or two *CYP2C19* loss-of-function alleles prescribed clopidogrel.

WHAT IS NEXT?

Strategies to more broadly incorporate genotyping into clinical care to inform antiplatelet therapy prescribing decisions after PCI, and to evaluate the impact on health care costs, warrant further investigation.

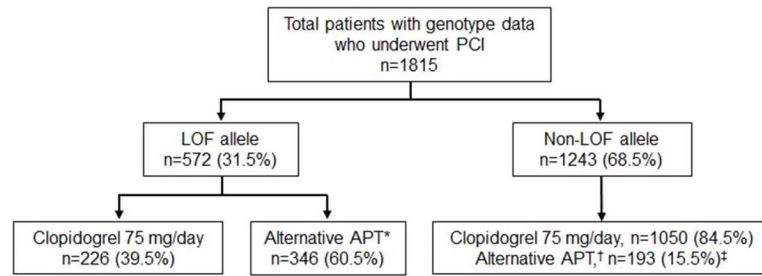


FIGURE 1. Study Population by *CYP2C19* Genotype Group and Antiplatelet Therapy

*Alternative therapy in patients with a LOF allele consisted of prasugrel (n=222), ticagrelor (n=116), or high dose clopidogrel (150 mg/day, n=2; 225 mg/day, n=6).

†Alternative therapy in the non-LOF group consisted of prasugrel (n=125) or ticagrelor (n=68).

‡p<0.001 for use of alternative therapy in the non-LOF group compared to the LOF group. APT, antiplatelet therapy; LOF, loss-of-function; PCI, percutaneous coronary intervention

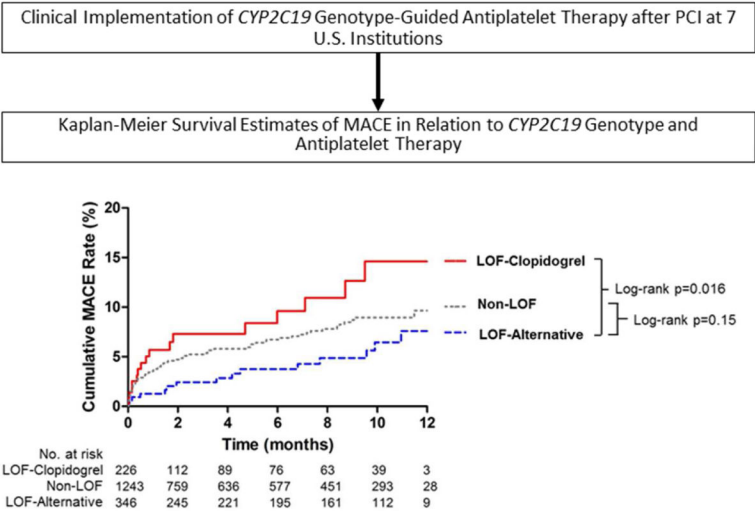


FIGURE 2, CENTRAL ILLUSTRATION. Outcomes with Clinical Implementation of *CYP2C19*-Guided Antiplatelet Therapy after PCI

Data are shown for patients with a *CYP2C19* loss-of-function (LOF) allele treated with clopidogrel (LOF-Clopidogrel), patients with a LOF allele treated with alternative antiplatelet drug therapy (LOF-Alternative), and patients without an LOF allele treated with either clopidogrel or alternative therapy (non-LOF). The unadjusted log-rank p-values for the LOF-Clopidogrel group compared to LOF-Alternative group and for the Non-LOF group compared to the LOF-Alternative group are provided. LOF, loss-of-function; MACE, major adverse cardiovascular events

TABLE 1

Patient Characteristics at the Time of Index PCI

Characteristic	All patients (n=1815)	LOF- Alternative (n=346)	LOF- Clopidogrel (n=226)	Non-LOF (n=1243)
Age, years	62.7 ± 11.8	61.4 ± 11.4	64.3 ± 11.7 *	62.8 ± 11.8 *
Male sex	1224 (67.4)	245 (70.8)	150 (66.4)	829 (66.7)
Race				
White	1416 (78.0)	267 (77.2)	172 (76.1)	977 (78.6)
Black	285 (15.7)	54 (15.6)	39 (17.3)	192 (15.4)
Other	114 (6.3)	25 (7.2)	15 (6.6)	74 (6.0)
BMI, kg/m ²	30.0 ± 6.2	30.1 ± 7.0	30.0 ± 6.5	29.8 ± 5.9
Current smoker	548 (30.2)	96 (27.7)	80 (35.4)	372 (29.9)
PCI indication				
ACS	1210 (66.7)	237 (68.5)	145 (64.2)	828 (66.6)
STEMI	350 (19.3)	75 (21.7)	33 (14.6)	242 (19.5)
Non-STEMI	513 (28.3)	96 (27.7)	72 (31.8)	345 (27.7)
Unstable angina	347 (19.1)	66 (19.1)	40 (17.7)	241 (19.4)
Stable coronary disease	553 (30.5)	99 (28.6)	70 (31.0)	384 (30.9)
Other/unknown	52 (2.8)	10 (2.9)	11 (4.9)	31 (2.5)
Pre-PCI P2Y ₁₂ inhibitor [†]				
Clopidogrel	1204 (66.3)	202 (58.4)	178 (78.8)	824 (66.3)
Prasugrel	235 (12.9)	68 (19.7)	6 (2.7)	161 (13.0)
Ticagrelor	218 (12.0)	47 (13.6)	23 (10.2)	148 (11.9)
Not available	158 (8.7)	29 (8.4)	19 (8.4)	110 (8.8)
PCI type [‡]				
Drug eluting stent	1518 (83.6)	293 (84.7)	182 (80.5)	1043 (83.9)
Bare metal stent	275 (15.2)	46 (13.3)	40 (17.7)	189 (15.2)
Balloon angioplasty	21 (1.2)	7 (2.0)	3 (1.3)	11 (0.9)
Medical history				
Hypertension	1449 (79.8)	260 (75.1)	183 (81.0)	1006 (80.9) *
Diabetes	691 (38.1)	110 (31.8)	93 (41.2) *	488 (39.3) *
Dyslipidemia	1229 (67.7)	236 (68.2)	154 (68.1)	839 (67.5)
Chronic Kidney Disease [§]	538 (29.6)	106 (30.6)	77 (34.1)	355 (28.6)
Myocardial infarction	470 (25.9)	86 (24.9)	68 (30.1)	316 (25.4)
Revascularization	779 (42.9)	137 (39.6)	103 (45.6)	539 (43.4)
Coronary artery bypass graft	313 (17.3)	61 (17.7)	43 (19.0)	209 (16.9)
Heart failure	252 (13.9)	42 (12.1)	37 (16.4)	173 (13.9)
Left ventricular EF (%) [?]	51.7 ± 11.9	52.4 ± 11.4	50.2 ± 12.8	51.8 ± 11.9
Stroke or TIA	183 (10.1)	24 (6.9)	36 (15.9) *	123 (9.9)

Characteristic	All patients (n=1815)	LOF- Alternative (n=346)	LOF- Clopidogrel (n=226)	Non-LOF (n=1243)
Peripheral vascular disease	155 (8.5)	24 (6.9)	28 (12.4) *	103 (8.3)
Atrial fibrillation/flutter	159 (8.8)	27 (7.8)	25 (11.1)	107 (8.6)
Gastrointestinal bleed	54 (3.0)	14 (4.1)	10 (4.4)	30 (2.4)
Discharge medication				
Aspirin	1782 (98.2)	342 (98.8)	220 (97.4)	1220 (98.2)
Proton pump inhibitor	586 (32.3)	110 (31.8)	72 (31.9)	404 (32.5)
Anticoagulant	152 (8.4)	22 (6.4)	26 (11.5) *	104 (8.4)
Statin	1686 (92.9)	329 (95.1)	210 (92.9)	1147 (92.3)
ACE inhibitor or ARB	1202 (66.2)	238 (68.8)	152 (67.3)	812 (65.3)
B-blocker	1539 (84.8)	285 (82.4)	181 (80.1)	1073 (86.3)

No. (%) or mean \pm SD

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; EF, ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack

LOF-Clopidogrel patients were those with at least 1 loss-of-function allele (i.e. *2, *3...) treated with clopidogrel

LOF-Alternative patients were those with at least 1 loss-of-function allele (i.e. *2, *3...) treated with prasugrel, ticagrelor, or high dose clopidogrel

Non-LOF patients were those with no loss-of-function allele: */*1, */*17, or */*17 genotype.

* p<0.05 compared to LOF-Alternative group

[†] Pre-PCI P2Y₁₂ inhibitor defined as drug used for loading or, if the drug used for loading was not reported, P2Y₁₂ inhibitor on admission was used.

[‡] One patient had a stent placed but no data were provided on type of stent

[§] Chronic kidney disease defined as an estimated creatinine clearance (based on the Cockcroft-Gault formula) <60 ml/min

[?] Left ventricular ejection fraction, as measured during cardiac catheterization, was available for 1,274 patients

TABLE 2
Patient Characteristics after Adjustment with Inverse Probability of Treatment Weights

Characteristic	LOF- Clopidogrel (n=226)	LOF- Alternative (n=346)	Standardized differences*	Non-LOF (n=1243)	LOF- Alternative (n=345)	Standardized differences*
Age	62.7 ± 11.7	62.5 ± 11.4	0.02	62.5 ± 11.8	62.3 ± 11.6	0.01
Male	150 (67.5)	237 (68.9)	0.03	836 (67.6)	229 (67.0)	0.01
Race						
White	166 (75.2)	263 (76.4)	0.03	968 (78.2)	266 (77.7)	0.01
Black	39 (17.6)	55 (15.9)	0.05	193 (15.6)	53 (15.6)	0.00
BMI	30.2 ± 6.3	30.1 ± 7.3	0.01	29.8 ± 5.9	29.8 ± 6.9	0.00
Current smoker	69 (31.4)	107 (31.2)	0.00	363 (29.4)	97 (28.5)	0.02
PCI indication						
Stable angina	65 (28.2)	100 (29.4)	0.03	376 (30.4)	101 (29.6)	0.02
ACS	148 (67.0)	232 (67.3)	0.01	828 (66.9)	233 (67.9)	0.02
Stent type						
Drug eluting	185 (84.3)	290 (83.8)	0.01	1040 (84.1)	290 (84.8)	0.02
Bare metal	34 (15.0)	48 (14.1)	0.03	182 (14.7)	48 (14.0)	0.02
Medical history						
Hypertension	168 (76.0)	273 (76.4)	0.01	986 (79.7)	271 (79.2)	0.01
Diabetes	81 (36.8)	121 (35.3)	0.03	466 (37.6)	124 (36.2)	0.03
Dyslipidemia	153 (69.1)	236 (68.5)	0.01	837 (67.6)	232 (67.7)	0.00
GFR †	74.0 ± 27.7	74.7 ± 31.5	0.02	74.5 ± 28.1	75.2 ± 31.6	0.02
MI	60 (27.1)	92 (26.8)	0.01	313 (25.4)	88 (25.8)	0.01
Revascularization	95 (43.2)	147 (42.9)	0.05	143 (41.8)	525 (42.4)	0.01
Heart failure	32 (14.8)	51 (14.8)	0.00	166 (13.5)	45 (13.2)	0.01
Stroke or TIA	23 (10.7)	33 (9.7)	0.03	114 (9.2)	28 (8.3)	0.03
PVD	21 (9.3)	31 (9.0)	0.01	99 (8.0)	26 (7.6)	0.01
Medication use						
Aspirin	217 (98.3)	339 (98.4)	0.01	1216 (98.2)	336 (98.2)	0.00
PPI	69 (31.4)	109 (31.7)	0.01	398 (32.2)	106 (30.9)	0.05

Characteristic	LOF- Clopidogrel (n=226)	LOF- Alternative (n=346)	Standardized differences*	Non-LOF (n=1243)	LOF- Alternative (n=345)	Standardized differences*
Anticoagulant	19 (8.9)	28 (8.2)	0.03	98 (8.0)	24 (7.3)	0.03
Statin	209 (94.3)	325 (94.5)	0.01	1149 (92.8)	319 (93.3)	0.02
ACEi/ARB	149 (67.4)	231 (67.3)	0.00	817 (66.0)	224 (65.4)	0.01
Beta blocker	180 (81.5)	282 (81.8)	0.01	1055 (85.3)	291 (85.0)	0.01

No. (%) or mean \pm SD

ACEi, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; GFR, glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PVD, peripheral vascular disease; TIA, transient ischemic attack

* Weighted absolute standardized differences are calculated using stabilized inverse probability of treatment weighting. All values are less than 0.1, which indicate elimination of imbalance between the two groups.

[†] Estimated creatinine clearance using Cockcroft-Gault formula

TABLE 3

Primary and Secondary Outcomes by *CYP2C19* Genotype and by Antiplatelet Therapy

Outcome	LOF-Clopidogrel (n=226)		LOF-Alternative (n=346)		Non-LOF (n=1243)		Adjusted HR (95% CI) for LOF-Clopidogrel vs LOF- Alternative	Adjusted HR (95% CI) for Non-LOF vs LOF- Alternative
	No. (%)	Event rate*	No. (%)	Event rate*	No. (%)	Event rate*		
MACE	18 (7.96)	23.4	16 (4.62)	8.7	74 (5.95)	13.7	2.26 (1.18–4.32)	1.14 (0.69–1.88)
Death	8 (3.54)	10.4	6 (1.73)	3.3	36 (2.90)	6.6	3.76 (1.37–10.35)	1.56 (0.68–3.56)
MI	11 (4.87)	14.3	9 (2.60)	4.9	38 (3.06)	7.0	1.85 (0.77–4.45)	1.00 (0.52–1.92)
Ischemic stroke	3 (1.33)	3.9	2 (0.58)	1.1	13 (1.05)	2.4	2.81 (0.43–18.03)	2.52 (0.49–12.91)
MACE plus other ischemic events [†]	25 (11.06)	32.5	28 (8.09)	15.2	106 (8.53)	19.6	1.82 (1.07–3.12)	1.09 (0.72–1.63)
Stent Thrombosis	4 (1.77)	5.2	4 (1.16)	2.2	13 (1.05)	2.4	1.68 (0.37–7.53)	1.01 (0.32–3.15)
Unstable angina	7 (3.10)	9.1	12 (3.47)	6.5	31 (2.49)	5.7	1.41 (0.55–3.64)	0.87 (0.44–1.70)

Unadjusted proportion of patients experiencing an event during follow-up (%), event rate (per 100-patient years), adjusted hazard ratio (HR) and 95% confidence interval (CI). The hazard ratio was adjusted with inverse probability weights derived from exposure propensity scores. Refer to Table 2 for variables included in the propensity score.

Event rates were calculated the number of events divided by follow-up time from index PCI to MACE or censoring in patient-years and are presented as medians.

The median length of follow-up was 7.3 (IQR 1.5–10.9), 1.8 (0.2–8.2), and 4.5 (0.5 to 9.7) months in the LOF-alternative, LOF-clopidogrel, and non-LOF groups, respectively (p<0.001).

LOF-Clopidogrel patients were those with at least 1 loss-of-function allele (i.e. (*2, *3...)/treated with clopidogrel

LOF-Alternative patients were those with at least 1 loss-of-function allele (i.e. (*2, *3...)/treated with prasugrel (n=222), ticagrelor (n=116), or high dose clopidogrel (n=8)

Non-LOF patients were those with no loss-of-function allele: */*1, */*17, or */*17/*17 genotypes.

* Median event rate expressed as events per 100 patient-years

[†] Composite of MACE (defined as first occurrence of myocardial infarction, ischemic stroke, or death) plus stent thrombosis and unstable angina